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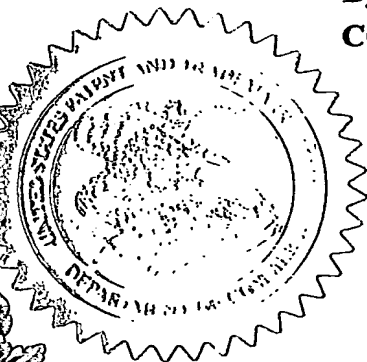
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<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max)					
Methods for Carbon Isotope Labeling Synthesis of Ketones and Amines by Suzuki Coupling Reactions using Carbon-Isotope Monoxide					
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Respectfully submitted,

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Date 12/24/2003

REGISTRATION NO.

45,629

(if appropriate)

Docket Number:

PH0390

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Docket No.

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**December 24, 2003**Examiner  
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To Be AssignedInvention: **Methods for Carbon Isotope Labeling Synthesis of Ketones and Amines by Suzuki Coupling Reactions using Carbon-Isotope Monoxide**

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Carbonylation reactions using [ $^{11}\text{C}$ ]carbon monoxide has a primary value for PET-tracer synthesis since biologically active substances often contain carbonyl groups or functionalities that can be derived from a carbonyl group. The syntheses are tolerant to most functional groups, which means that complex building blocks can be assembled in the carbonylation step to yield the target compound. This is particularly valuable in PET-tracer synthesis where the unlabeled substrates should be combined with the labeled precursor as late as possible in the reaction sequence, in order to decrease synthesis-time and thus optimize the uncorrected radiochemical yield.

When compounds are labeled with  $^{11}\text{C}$ , it is usually important to maximize specific radioactivity. In order to achieve this, the isotopic dilution and the synthesis time must be minimized. Isotopic dilution from atmospheric carbon dioxide may be substantial when [ $^{11}\text{C}$ ]carbon dioxide is used in a labeling reaction. Due to the low reactivity and atmospheric concentration of carbon monoxide (0.1 ppm vs.  $3.4 \times 10^4$  ppm for  $\text{CO}_2$ ), this problem is reduced with reactions using [ $^{11}\text{C}$ ]carbon monoxide.

The synthesis of [ $^{11}\text{C}$ ]carbon monoxide from [ $^{11}\text{C}$ ]carbon dioxide using a heated column containing reducing agents such as zinc, charcoal or molybdenum has been described previously in several publications. Although [ $^{11}\text{C}$ ]carbon monoxide was one of the first  $^{11}\text{C}$ -labelled compounds to be applied in tracer experiments in human, it has until recently not found any practical use in the production of PET-tracers. One reason for this is the low solubility and relative slow reaction rate of [ $^{11}\text{C}$ ]carbon monoxide which causes low trapping efficiency in reaction media. The general procedure using precursors such as [ $^{11}\text{C}$ ]methyl iodide, [ $^{11}\text{C}$ ]hydrogen cyanide or [ $^{11}\text{C}$ ]carbon dioxide is to transfer the radioactivity in a gas-phase, and trap the radioactivity by leading the gas stream through a reaction medium. Until recently this has been the only accessible procedure to handle [ $^{11}\text{C}$ ]carbon monoxide in labeling synthesis. With this approach, the main part of the labeling syntheses with [ $^{11}\text{C}$ ]carbon monoxide can be expected to give a very low yield or fail completely.

There are only a few examples of practically valuable  $^{11}\text{C}$ -labelling syntheses using high pressure techniques (> 300 bar). In principal, high pressures can be

utilized for increasing reaction rates and minimizing the amounts of reagents. One problem with this approach is how to confine the labeled precursor in a small high-pressure reactor. Another problem is the construction of the reactor. If a common column type of reactor is used (i.e. a cylinder with tubing attached to each end), the gas-phase will actually become efficiently excluded from the liquid phase at pressurization. The reason is that the gas-phase, in contracted form, will escape into the attached tubing and away from the bulk amount of the liquid reagent.

The cold-trap technique is widely used in the handling of  $^{11}\text{C}$ -labelled precursors, particularly in the case of  $^{11}\text{C}$  carbon dioxide. The procedure has, however, only been performed in one single step and the labeled compound was always released in a continuous gas-stream simultaneous with the heating of the cold-trap. Furthermore, the volume of the material used to trap the labeled compound has been relative large in relation to the system to which the labeled compound has been transferred. Thus, the option of using this technique for radical concentration of the labeled compound and miniaturization of synthesis systems has not been explored. This is especially noteworthy in view of the fact that the amount of a  $^{11}\text{C}$ -labelled compound usually is in the range 20-60 nmol.

Recent technical development for the production and use of  $^{11}\text{C}$  carbon monoxide has made this compound useful in labeling synthesis. WO 02/102711 describes a system and a method for the production and use of a carbon-isotope monoxide enriched gas-mixture from an initial carbon-isotope dioxide gas mixture.  $^{11}\text{C}$  carbon monoxide may be obtained in high radiochemical yield from cyclotron produced  $^{11}\text{C}$  carbon dioxide and can be used to yield target compounds with high specific radioactivity. This reactor overcomes the difficulties listed above and is useful in synthesis of  $^{11}\text{C}$ -labelled compounds using  $^{11}\text{C}$  carbon monoxide in palladium or selenium mediated reaction. With such method, a broad array of carbonyl compounds can be labeled (Kihlberg, T.; Langstrom, B. J., *Org. Chem.* 64, 1999, 9201-9205; Kihlberg, T., Karimi, F., Langstrom, B., *J. Org. Chem.* 67, 2002, 3687-3692).

Such labeled carbonyl compounds have opened an avenue to synthesize a number of pharmaceutically important tracers for applications with PET. It is notable

that ketones are widely used as building blocks for biologically important molecules and be used as reaction precursors or PET tracers by labeling with carbon isotope. Amines are an important class of compounds since the biological activities of many pharmaceutical agents depend on amine functionality. Thus, carbon-isotope labeled amines can be used as important and useful PET tracers.

Transitional metal-catalyzed carbonylations using electrophiles, carbon monoxide and organostannanes (Stille coupling) or organoboron compounds (Suzuki coupling) are approaches that are used frequently for synthesis of ketones. In  $^{11}\text{C}$  labeling chemistry, the Stille carbonylation has been subjected to a number of studies, but the Suzuki carbonylation has been used rarely. For example, Stille coupling has been used to synthesize a series of  $^{11}\text{C}$ -labeled ketones (Lindstrom, P., Kihlberg, T., Langstrom, B., J. Chem. Soc. Perkin Trans. 1, 1997, 2701-2706). However, one disadvantage of using such an approach is the use of highly toxic organostannanes compounds.

Separately, synthesis of  $^{11}\text{C}$ -labeled benzophenone using organoboranes and iodobenzene (Suzuki coupling) was reported (Zeisler, S., Nader, M. Theobald, A. and Oberdorfer, F., Appl. Radiat. Isot. 1997, 48, 1091-1095). However, the method of  $^{11}\text{C}$  carbon monoxide production used in this report suffers the low specific radioactivity described above. Thus, there is a need for an increased specific radioactivity used in Suzuki coupling reactions.

Efficient methods of synthesizing  $^{11}\text{C}$ -labeled amines are also yet to be explored. One report has previously been published about the synthesis of  $^{11}\text{C}$ -labeled amines by reductive amination of carboxylic acids and  $^{11}\text{C}$  magnesium halide carboxylates (Perrio-Huard, C. et al, J. Chem. Soc. Perkin Trans. 1, 2000, 311-316). However, such a method uses  $^{11}\text{C}$  carbon dioxide as the labeled precursor. Thus, such a method is not optimal.

Therefore, there is a need for new and improved methods of synthesizing carbon-isotope labeled ketones and amines as reaction precursors or PET tracers by using  $^{11}\text{C}$  carbon monoxide. It would further increase the utility of  $^{11}\text{C}$  carbon monoxide in preparing useful PET tracers.

Discussion or citation of a reference herein shall not be construed as an admission that such reference is prior art to the present invention.

### Summary of the Invention

The present invention provides a method for labeling synthesis of ketones via Suzuki coupling, comprising:

- (a) providing a high pressure reaction chamber having a liquid inlet and a gas inlet in a bottom surface thereof,
- (b) providing a solution to be labeled comprising a triflate, a boronic acid mixed with a transition metal complex,
- (c) introducing a carbon-isotope monoxide enriched gas-mixture into the reaction chamber via the gas inlet,
- (d) introducing at high-pressure said solution mixed with transition metal complex into the reaction chamber via the liquid inlet,
- (e) waiting a predetermined time while the labeling synthesis occur, and
- (f) removing the labeled ketones from the reaction chamber.

The present invention also provides carbon-isotope labeled ketones synthesized by the method of the instant invention.

The present invention further provides a method for labeling synthesis of amines comprising reductively aminate carbon-isotope-labeled ketones obtained by a method of the instant invention using amines,  $\text{TiCl}_4$  and  $\text{NaBH}_3\text{CN}$ .

In yet another embodiment, the invention also provides carbon-isotope labeled amines synthesized by the method of the instant invention. In still another embodiment, the invention provides kits for use as PET tracers comprising such  $[^{11}\text{C}]$ -labeled ketones and/or amines.

### Brief Description of the Figures

Fig. 1 shows a flow chart over the method according to the invention.



Fig. 2 is a schematic view of a carbon-isotope monoxide production and labeling-system according to the invention.

5 Fig. 3a and 3b show alternative embodiments of a reaction chamber according to the invention.

### Detailed Description of the Invention

10 One object of the invention is to provide a method and a system for production of and use of carbon-isotope monoxide in labeling synthesis that overcomes the drawbacks of the prior art devices. This is achieved by the method and system described in the invention.

15 One advantage with such a method and system is that nearly quantitative conversion of carbon-isotope monoxide into labeled products can be accomplished.

20 There are several other advantages with the present method and system. The high-pressure technique makes it possible to use low boiling solvents such as diethyl ether at high temperatures (e.g. 200 °C). The use of a closed system consisting of materials that prevents gas diffusion, increases the stability of sensitive compounds and could be advantageous also with respect to Good Manufacturing Practice (GMP).

25 Still other advantages are achieved in that the resulting labeled compound is highly concentrated, and that the miniaturization of the synthesis system facilitates automation, rapid synthesis and purification, and optimization of specific radioactivity through minimization of isotopic dilution.

30 Most important is the opening of completely new synthesis possibilities, as exemplified by the present invention.

Embodiments of the invention will now be described with reference to the figures.

The term carbon-isotope that is used throughout this application preferably refers to  $^{11}\text{C}$ , but it should be understood that  $^{11}\text{C}$  may be substituted by other carbon-isotopes, such as  $^{13}\text{C}$  and  $^{14}\text{C}$ , if desired.

Fig. 1 shows a flow chart over the method according to the invention, which firstly comprises production of a carbon-isotope monoxide enriched gas-mixture and secondly a labeling synthesis procedure. More in detail the production part of the method comprises the steps of:

- Providing carbon-isotope dioxide in a suitable carrier gas of a type that will be described in detail below.

- Converting carbon-isotope dioxide to carbon-isotope monoxide by introducing said gas mixture in a reactor device which will be described in detail below.

- Removing traces of carbon-isotope dioxide by flooding the converted gas-mixture through a carbon dioxide removal device wherein carbon-isotope dioxide is trapped but not carbon-isotope monoxide nor the carrier gas. The carbon dioxide removal device will be described in detail below.

- Trapping carbon-isotope monoxide in a carbon monoxide trapping device, wherein carbon-isotope monoxide is trapped but not said carrier gas. The carbon monoxide trapping device will be described in detail below.

- Releasing said trapped carbon-isotope monoxide from said trapping device, whereby a volume of carbon-isotope monoxide enriched gas-mixture is achieved.

The production step may further comprise a step of changing carrier gas for the initial carbon-isotope dioxide gas mixture if the initial carbon-isotope dioxide gas mixture is comprised of carbon-isotope dioxide and a first carrier gas not suitable as carrier gas for carbon monoxide due to similar molecular properties or the like, such as nitrogen. More in detail the step of providing carbon-isotope dioxide in a suitable second carrier gas such as He, Ar, comprises the steps of:

- Flooding the initial carbon-isotope dioxide gas mixture through a carbon dioxide trapping device, wherein carbon-isotope dioxide is trapped but not said first carrier gas. The carbon dioxide trapping device will be described in detail below.

- Flushing said carbon dioxide trapping device with said suitable second carrier gas to remove the remainders of said first carrier gas.

- Releasing said trapped carbon-isotope dioxide in said suitable second carrier gas.

The labeling synthesis step that may follow the production step utilizes the produced carbon-isotope monoxide enriched gas-mixture as labeling reactant. More in detail the step of labeling synthesis comprises the steps of:

- Providing a high pressure reaction chamber having a liquid reagent inlet and a labeling reactant inlet in a bottom surface thereof. The reaction chamber will be described in detail below.

- Providing a solution to be labeled comprising a triflate, a boronic acid mixed with a transition metal complex.

- Introducing the carbon-isotope monoxide enriched gas-mixture into the reaction chamber via the labeling reactant inlet.

- Introducing, at high pressure, said solution mixed with transition metal complex into the reaction chamber via the liquid reagent inlet.

- Waiting a predetermined time while the labeling synthesis occurs.

- Removing the solution of labeled compound from the reaction chamber.

10 The solution to be labeled may further comprise lithium bromide to facilitate the reaction. The transition metal complex is preferably a palladium complex.

The step of waiting a predetermined time may further comprise adjusting the temperature of the reaction chamber such that the labeling synthesis is enhanced.

15 Fig. 2 schematically shows a [ $^{11}\text{C}$ ]carbon dioxide production and labeling-system according to the present invention. The system is comprised of three main blocks, each handling one of the three main steps of the method of production and labeling:

20 Block A is used to perform a change of carrier gas for an initial carbon-isotope dioxide gas mixture, if the initial carbon-isotope dioxide gas mixture is comprised of carbon-isotope dioxide and a first carrier gas not suitable as carrier gas for carbon monoxide.

25 Block B is used to perform the conversion from carbon-isotope dioxide to carbon-isotope monoxide, and purify and concentrate the converted carbon-isotope monoxide gas mixture.

Block C is used to perform the carbon-isotope monoxide labeling synthesis.

30

Block A is normally needed due to the fact that carbon-isotope dioxide usually is produced using the  $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$  reaction in a target gas containing nitrogen and 0.1% oxygen, bombarded with 17 MeV protons, whereby the initial carbon-isotope

dioxide gas mixture comprises nitrogen as carrier gas. However, compared with carbon monoxide, nitrogen show certain similarities in molecular properties that makes it difficult to separate them from each other, e.g. in a trapping device or the like, whereby it is difficult to increase the concentration of carbon-isotope monoxide in such a gas mixture. Suitable carrier gases may instead be helium, argon or the like. Block A can also be used to change the pressure of the carrier gas (e.g. from 1 to 4 bar), in case the external system does not tolerate the gas pressure needed in block B and C. In an alternative embodiment the initial carbon-isotope dioxide gas mixture is comprised of carbon-isotope dioxide and a first carrier gas that is well suited as carrier gas for carbon monoxide, whereby the block A may be simplified or even excluded.

According to a preferred embodiment (Fig. 2), block A is comprised of a first valve V1, a carbon dioxide trapping device 8, and a second valve V2.

The first valve V1 has a carbon dioxide inlet 10 connected to a source of initial carbon-isotope dioxide gas mixture 12, a carrier gas inlet 14 connected to a source of suitable carrier gas 16, such as helium, argon and the like. The first valve V1 further has a first outlet 18 connected to a first inlet 20 of the second valve V2, and a second outlet 22 connected to the carbon dioxide trapping device 8. The valve V1 may be operated in two modes A, B, in mode A the carbon dioxide inlet 10 is connected to the first outlet 18 and the carrier gas inlet 14 is connected to the second outlet 22, and in mode B the carbon dioxide inlet 10 is connected to the second outlet 22 and the carrier gas inlet 14 is connected to the first outlet 18.

In addition to the first inlet 20, the second valve V2 has a second inlet 24 connected to the carbon dioxide trapping device 8. The second valve V2 further has a waste outlet 26, and a product outlet 28 connected to a product inlet 30 of block B. The valve V2 may be operated in two modes A, B, in mode A the first inlet 20 is connected to the waste outlet 26 and the second inlet 24 is connected to the product outlet 28, and in mode B the first inlet 20 is connected to the product outlet 28 and the second inlet 24 is connected to the waste outlet 26.

The carbon dioxide trapping device 8 is a device wherein carbon dioxide is trapped but not said first carrier gas, which trapped carbon dioxide thereafter may be

released in a controlled manner. This may preferably be achieved by using a cold trap, such as a column containing a material which in a cold state, (e.g.  $-196^{\circ}\text{C}$  as in liquid nitrogen or  $-186^{\circ}\text{C}$  as in liquid argon) selectively trap carbon dioxide and in a warm state (e.g.  $+50^{\circ}\text{C}$ ) releases the trapped carbon dioxide. (In this text the  
5 expression "cold trap" is not restricted to the use of cryogenics. Thus, materials that traps the topical compound at room temperature and release it at a higher temperature are included). Examples of suitable material are silica and porapac Q®. The trapping behavior of a silica-column or a porapac-column is related to dipole-dipole interactions or possibly Van der Waal interactions. The said column 8 is preferably  
10 formed such that the volume of the trapping material is to be large enough to efficiently trap ( $>95\%$ ) the carbon-isotope dioxide, and small enough not to prolong the transfer of trapped carbon dioxide to block B. In the case of porapac Q® and a flow of 100 ml nitrogen/ min, the volume should be 50-150  $\mu\text{l}$ . The cooling and heating of the carbon dioxide trapping device 8 may further be arranged such that it is  
15 performed as an automated process, e.g. by automatically lowering the column into liquid nitrogen and moving it from there into a heating arrangement.

According to the preferred embodiment of Fig. 2, block B is comprised of a reactor device 32 in which carbon-isotope dioxide is converted to carbon-isotope  
20 monoxide, a carbon dioxide removal device 34, a check-valve 36, and a carbon monoxide trapping device 38, which all are connected in a line.

In the preferred embodiment the reactor device 32 is a reactor furnace comprising a material that when heated to the right temperature interval converts  
25 carbon-isotope dioxide to carbon-isotope monoxide. A broad range of different materials with the ability to convert carbon dioxide into carbon monoxide may be used, e.g. zinc or molybdenum or any other element or compound with similar reductive properties. If the reactor device 32 is a zinc furnace it should be heated to  $350$  to  $400^{\circ}\text{C}$ , and it is important that the temperature is regulated with high precision.  
30 The melting point of zinc is  $420^{\circ}\text{C}$  and the zinc-furnace quickly loses its ability to transform carbon dioxide into carbon monoxide when the temperature reaches over  $410^{\circ}\text{C}$ , probably due to changed surface properties. The material should be efficient in relation to its amount to ensure that a small amount can be used, which will

minimize the time needed to transfer radioactivity from the carbon dioxide trapping device 8 to the subsequent carbon monoxide trapping device 38. The amount of material in the furnace should be large enough to ensure a practical life-time for the furnace (at least several days). In the case of zinc granulates, the volume should be  
5 100-1000  $\mu$ l.

The carbon dioxide removal device 34 is used to remove traces of carbon-isotope dioxide from the gas mixture exiting the reactor device 32. In the carbon dioxide removal device 34, carbon-isotope dioxide is trapped but not carbon-isotope  
10 monoxide nor the carrier gas. The carbon dioxide removal device 34 may be comprised of a column containing ascarite® (i.e. sodium hydroxide on silica). Carbon-isotope dioxide that has not reacted in the reactor device 32 is trapped in this column (it reacts with sodium hydroxide and turns into sodium carbonate), while carbon-isotope monoxide passes through. The radioactivity in the carbon dioxide  
15 removal device 34 is monitored as a high value indicates that the reactor device 32 is not functioning properly.

Like the carbon dioxide trapping device 8, the carbon monoxide trapping device 38, has a trapping and a releasing state. In the trapping state carbon-isotope  
20 monoxide is selectively trapped but not said carrier gas, and in the releasing state said trapped carbon-isotope monoxide is released in a controlled manner. This may preferably be achieved by using a cold trap, such as a column containing silica or materials of similar properties, such as molecular sieves. Such a cold trap selectively traps carbon monoxide in a cold state below  $-100^{\circ}\text{C}$ , e.g.  $-196^{\circ}\text{C}$  as in liquid nitrogen  
25 or  $-186^{\circ}\text{C}$  as in liquid argon, and releases the trapped carbon monoxide in a warm state (e.g.  $+50^{\circ}\text{C}$ ). The trapping behavior of the silica-column is related to dipole-dipole interactions or possibly Van der Waal interactions. The ability of the silica-column to trap carbon-isotope monoxide is reduced if the helium, carrying the radioactivity, contains nitrogen. A rationale is that since the physical properties of  
30 nitrogen are similar to carbon monoxide, nitrogen competes with carbon monoxide for the trapping sites on the silica.

According to the preferred embodiment of Fig. 2, block C is comprised of a first and a second reaction chamber valve V3 and V4, the aforementioned reaction chamber 50, a reagent valve V5, an injection loop 70 and a solvent valve V6.

5       The first reaction chamber valve V3 has a gas mixture inlet 40 connected to the carbon monoxide trapping device 38, a stop position 42, a collection outlet 44, a waste outlet 46, and a reaction chamber connection port 48 connected to a gas inlet 52 of the reaction chamber 50. The first reaction chamber valve V3 has four modes of operation A to D. The reaction chamber connection port 48 is: in mode A connected.  
10      to the gas mixture inlet 40, in mode B connected to the stop position 42, in mode C connected to the collection outlet 44, and in mode D connected to the waste outlet 46.

      The reaction chamber 50 (micro-autoclave) has a gas inlet 52 and a liquid inlet 54, which are arranged such that they terminate at the bottom surface of the chamber.  
15      Gas inlet 52 may also be used as product outlet after the labeling is finished. During operation the carbon-isotope monoxide enriched gas mixture is introduced into the reaction chamber 50 through the gas inlet 52, where after the solution to be labeled with transition metal complex at high pressure enters the reaction chamber 50 through the liquid inlet 54. Fig. 3a and 3b shows schematic views of two preferred reaction  
20      chambers 50 in cross section. Fig 3a is a cylindrical chamber which is fairly easy to produce, whereas the spherical chamber of fig. 3b is the most preferred embodiment, as the surface area to volume-ratio of the chamber is further minimized. A minimal surface area to volume-ratio optimizes the recovery of labeled product and minimizes possible reactions with the surface material. Due to the "diving-bell construction" of  
25      the reaction chamber 50, both the gas inlet 52 and the liquid inlet 54 becomes liquid-filled and the reaction chamber 50 is filled from the bottom upwards. The gas-volume containing the carbon-isotope monoxide is thus trapped and given efficient contact with the reaction mixture. Since the final pressure of the liquid is approximately 80 times higher than the original gas pressure, the final gas volume will be less than 2 %  
30      of the liquid volume according to the general gas-law. Thus, a pseudo one-phase system will result. In the instant application, the term "pseudo one-phase system" means a closed volume with a small surface area to volume-ratio containing >96% liquid and <4% gas at pressures exceeding 200 bar. In most syntheses the transfer of carbon monoxide from the gas-phase to the liquid phase will probably not be the rate



limiting step. After the labeling is finished the labeled volume is nearly quantitatively transferred from the reaction chamber by the internal pressure via the gas inlet/product outlet 52 and the first reaction chamber valve V3 in position C.

5       The second reaction chamber valve V4 has a reaction chamber connection port 56, a waste outlet 58, and a reagent inlet 60. The second reaction chamber valve V4 has two modes of operation A and B. The reaction chamber connection port 56 is: in mode A connected to the waste outlet 58, and in mode B it is connected to the reagent inlet 60.

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      The reagent valve V5, has a reagent outlet 62 connected to the reagent inlet 60 of the second reaction chamber valve V4, an injection loop inlet 64 and outlet 66 between which the injection loop 70 is connected, a waste outlet 68, a reagent inlet 71 connected to a reagent source, and a solvent inlet 72. The reagent valve V5, has two  
15   modes of operation A and B. In mode A the reagent inlet 71 is connected to the injection loop inlet 64, and the injection loop outlet 66 is connected to the waste outlet 68, whereby a reagent may be fed into the injection loop 70. In mode B the solvent inlet 72 is connected to the injection loop inlet 64, and the injection loop outlet 66 is connected to the reagent outlet 62, whereby reagent stored in the injection loop 70  
20   may be forced via the second reaction chamber valve V4 into the reaction chamber 50 if a high pressure is applied on the solvent inlet 72.

      The solvent valve V6, has a solvent outlet 74 connected to the solvent inlet 72 of the reagent valve V5, a stop position 76, a waste outlet 78, and a solvent inlet 80  
25   connected to a solvent supplying HPLC-pump (High Performance Liquid Chromatography) or any liquid-pump capable of pumping organic solvents at 0-10 ml/ min at pressures up to 400 bar (not shown). The solvent valve V6, has two modes of operation A and B. In mode A the solvent outlet 74 is connected to the stop position 76, and the solvent inlet 80 is connected to the waste outlet 78. In mode B the  
30   solvent outlet 74 is connected to the solvent inlet 80, whereby solvent may be pumped into the system at high pressure by the HPLC-pump.

Except for the small volume of silica in the carbon monoxide trapping device 38, an important difference in comparison to the carbon dioxide trapping device 8, as well as to all related prior art, is the procedure used for releasing the carbon monoxide. After the trapping of carbon monoxide on carbon monoxide trapping device 8, valve V3 is changed from position A to B to stop the flow from the carbon monoxide trapping device 38 and increase the gas-pressure on the carbon monoxide trapping device 38 to the set feeding gas pressure (3-5 bar). The carbon monoxide trapping device 38 is then heated to release the carbon monoxide from the silica surface while not significantly expanding the volume of carbon monoxide in the carrier gas. Valve V4 is changed from position A to B and valve V3 is then changed from position B to A. At this instance the carbon monoxide is rapidly and almost quantitatively transferred in a well-defined micro-plug into the reaction chamber 50. Micro-plug is defined as a gas volume less than 10% of the volume of the reaction chamber 50, containing the topical substance (e.g. 1-20  $\mu$ L). This unique method for efficient mass-transfer to a small reaction chamber 50, having a closed outlet, has the following prerequisites:

- A micro-column 38 defined as follows should be used. The volume of the trapping material (e.g. silica) should be large enough to efficiently trap (>95%) the carbon-isotope monoxide, and small enough (< 1% of the volume of a subsequent reaction chamber 50) to allow maximal concentration of the carbon-isotope monoxide. In the case of silica and a reaction chamber 50 volume of 200  $\mu$ L, the silica volume should be 0.1-2  $\mu$ L.
- The dead volumes of the tubing and valve(s) connecting the silica column and the reaction chamber 50 should be minimal (<10% of the micro-autoclave volume).
- The pressure of the carrier gas should be 3-5 times higher than the pressure in the reaction chamber 50 before transfer (1 atm.).

In one specific preferred embodiment specifications, materials and components are chosen as follows. High pressure valves from Valco®, Reodyne® or

Cheminert® are used. Stainless steel tubing with o.d. 1/16" is used except for the connections to the porapac-column 8, the silica-column 38 and the reaction chamber 50 where stainless steel tubing with o.d. 1/32" are used in order to facilitate the translation movement. The connections between V1, V2 and V3 should have an inner diameter of 0.2-1 mm. The requirement is that the inner diameter should be large enough not to obstruct the possibility to achieve the optimal flow of He (2-50 ml/min) through the system, and small enough not to prolong the time needed to transfer the radioactivity from the porapac-column 8 to the silica-column 38. The dead volume of the connection between V3 and the autoclave should be minimized (< 10% of the autoclave volume). The inner diameter (0.05-0.1 mm) of the connection must be large enough to allow optimal He flow (2-50 ml/min). The dead volume of the connection between V4 and V5 should be less than 10% of the autoclave volume.

When column 8 is a porapac-column, it is preferably comprised of a stainless steel tube (o.d.= 1/8", i.d.= 2 mm, l= 20 mm) filled with Porapac Q® and fitted with stainless steel screens. The silica-column 38 preferably is comprised of a stainless steel tube (o.d.= 1/16", i.d.= 0.1 mm) with a cavity (d=1 mm, h= 1 mm, V= 0.8 µl) in the end. The cavity is filled with silica powder (100/80 mesh) of GC-stationary phase type. The end of the column is fitted against a stainless steel screen.

It should be noted that a broad range of different materials could be used in the trapping devices. If a GC-material is chosen, the criterions should be good retardation and good peak-shape for carbon dioxide and carbon monoxide respectively. The latter will ensure optimal recovery of the radioactivity.

Below a detailed description is given of a method of producing carbon-isotope using an exemplary system as described above.

Preparations of the system are performed by the steps 1 to 5:

1. V1 in position A, V2 in position A, V3 in position A, V4 in position A, helium flow on with a max pressure of 5 bar. With this setting, the helium flow goes through the [<sup>11</sup>C] carbon dioxide trapping column, the zinc furnace, the [<sup>11</sup>C] carbon monoxide trapping column, the reaction chamber 50 and out through V4. The system is conditioned, the reaction chamber 50 is rid of solvent and it

can be checked that helium can be flowed through the system with at least 10 ml/min.

2. The zinc-furnace is turned on and set at 400 °C.
3. The [ $^{11}\text{C}$ ] carbon dioxide and [ $^{11}\text{C}$ ] carbon monoxide trapping columns are cooled with liquid nitrogen. At -196 °C, the porapac-and silica-column efficiently traps carbon-isotope dioxide and carbon-isotope monoxide respectively.
4. V5 in position A (load). The injection loop (250  $\mu\text{l}$ ), attached to V5, is loaded with the reaction mixture.
5. The HPLC-pump is attached to a flask with freshly distilled THF (or other high quality solvent) and primed. V6 in position A.

Production of carbon-isotope dioxide may be performed by the steps 6 to 7:

6. Carbon-isotope dioxide is produced using the  $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$  reaction in a target gas containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA, Oxygen 4.8), bombarded with 17 MeV protons.
7. The carbon-isotope dioxide is transferred to the apparatus using nitrogen with a flow of 100 ml/min.

Synthesis of carbon-isotope may thereafter be performed by the steps 8 to 16.

8. V1 in position B and V2 in position B. The nitrogen flow containing the carbon-isotope dioxide is now directed through the porapac-column (cooled to -196 °C) and out through a waste line. The radioactivity trapped in the porapac-column is monitored.
9. When the radioactivity has peaked, V1 is changed to position A. Now a helium flow is directed through the porapac-column and out through the waste line. By this operation the tubings and the porapac-column are rid of nitrogen.
10. V2 in position A and the porapac-column is warmed to about 50 °C. The radioactivity is now released from the porapac-column and transferred with a

helium flow of 10 ml/ min into the zinc-furnace where it is transformed into carbon-isotope monoxide.

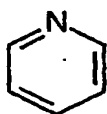
11. Before reaching the silica-column (cooled to  $-196^{\circ}\text{C}$ ), the gas flow passes the ascarite-column. The carbon-isotope monoxide is now trapped on the silica-column. The radioactivity in the silica-column is monitored and when the value has peaked, V3 is set to position B and then V4 is set to position B.
12. The silica-column is heated to approximately  $50^{\circ}\text{C}$ , which releases the carbon-isotope monoxide. V3 is set to position A and the carbon-isotope monoxide is transferred to the reaction chamber 50 within 15 s.
13. V3 is set to position B, V5 is set to position B, the HPLC-pump is turned on (flow 7 ml/ min) and V6 is set to position B. Using the pressurized THF (or other solvent), the reaction mixture is transferred to the reaction chamber 50. When the HPLC-pump has reached its set pressure limit (e.g 40 Mpa), it is automatically turned off and then V6 is set to position A.
14. The reaction chamber 50 is moved into the cavity of a heating block containing a high boiling liquid (e.g. polyethylene glycol or mineral oil). The temperature of the heating block is usually in the range of  $100\text{-}200^{\circ}\text{C}$ .
15. After a sufficient reaction-time (usually 5 min), V3 is set to position C and the content of the reaction chamber 50 is transferred to a collection vial.
16. The reaction chamber 50 can be rinsed by the following procedure: V3 is set to position B, the HPLC-pump is turned on, V6 is set to position B and when maximal pressure is reached V6 is set to position A and V3 is set to position 3 thereby transferring the rinse volume to the collection vial.

With the recently developed fully automated version of the reaction chamber 50 system according to the invention, the value of  $[^{11}\text{C}]$ carbon monoxide as a precursor for  $^{11}\text{C}$ -labelled tracers has become comparable with  $[^{11}\text{C}]$ methyl iodide. Currently,  $[^{11}\text{C}]$ methyl iodide is the most frequently used  $^{11}\text{C}$ -precursor due to ease in production and handling and since groups suitable for labeling with  $[^{11}\text{C}]$ methyl iodide (e.g. hetero atom bound methyl groups) are common among biologically active substances. Carbonyl groups, that can be conveniently labeled with  $[^{11}\text{C}]$ carbon

monoxide, are also common among biologically active substances. In many cases, due to metabolic events in vivo, a carbonyl group may even be more advantageous than a methyl group as labeling position. The use of [ $^{11}\text{C}$ ]carbon monoxide for production of PET-tracers may thus become an interesting complement to [ $^{11}\text{C}$ ]methyl iodide.

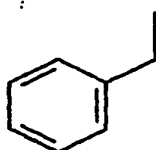
- 5 Furthermore, through the use of similar technology, this method will most likely be applicable for synthesis of  $^{13}\text{C}$  and  $^{14}\text{C}$  substituted compounds.

The main advantage of the present invention is to overcome the limitations of current carbonylation reaction labeling synthesis and provide a new efficient method of synthesizing [ $^{11}\text{C}$ ] ketones by Suzuki coupling reactions using [ $^{11}\text{C}$ ] carbon  
 10 monoxide and a solution comprising a triflate and a boronic acid mixed with a transition metal complex for the desired labeled compound. It further provides a new method of synthesizing [ $^{11}\text{C}$ ] amines by reductively aminating [ $^{11}\text{C}$ ] ketones obtained in the present invention using amines,  $\text{TiCl}_4$  and  $\text{NaBH}_3\text{CN}$ . The levels specific  
 15 radioactivity are high using the method of the instant invention. Triflates used as precursors in the instant invention have a formula  $\text{R1-OTf}$ , wherein R1 is linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl. Preferably, R1 is selected from  $\text{C}_6\text{H}_5$ ,  $4\text{-CH}_3\text{O-C}_6\text{H}_4$ ,  $4\text{-CH}_3\text{-C}_6\text{H}_4$ ,  $4\text{-NO}_2\text{-C}_6\text{H}_4$ ,  $\text{C}_{10}\text{H}_7$  or



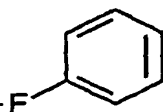
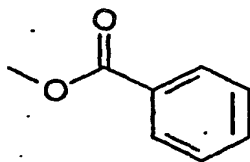
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Boronic acids used in this invention have a formula  $\text{RB(OH)}_2$ , wherein R is linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl. Preferably, R can be



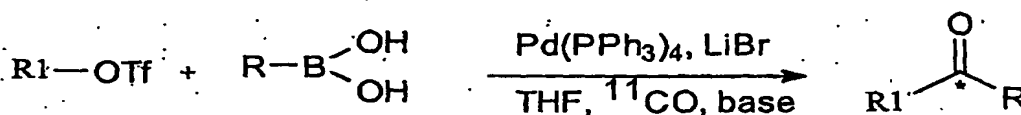
selected from phenyl, methyl,

25



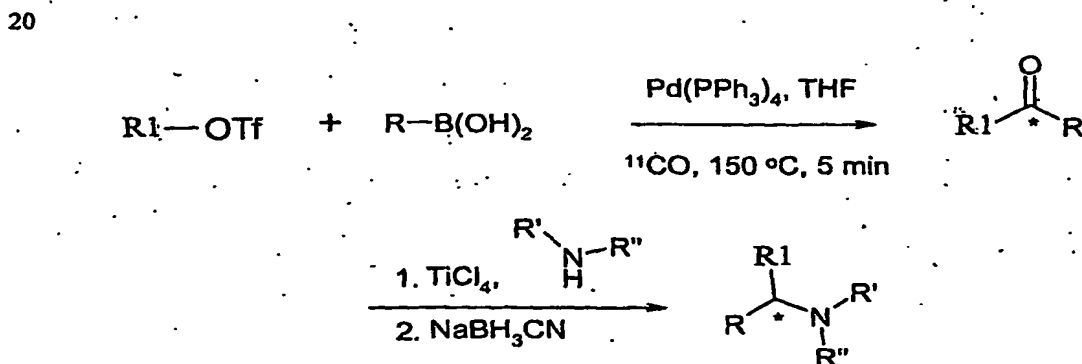
, or theinyl. The resultant labeled ketones have formula of  $R1-C^*O-R$ , wherein \* is labeled carbon position, and  $R1$  and  $R$  are as defined above.

- 5 A preferred reaction scheme for the synthesis of labeled ketones is illustrated below:



- 10 In this reaction, the preferred transition metal complex is a palladium complex. Lithium bromide may be optionally added to facilitate the reaction. Different bases may be employed to improve the radiochemical yields.

- Another embodiment of the present invention is the new method of synthesizing  $^{11}\text{C}$ -labeled amines from  $^{11}\text{C}$ -labeled ketones obtained by the methods of the instant invention. After  $^{11}\text{C}$ -labeled ketones are collected in a collection vial according the methods of the instant invention, they may be further reductive aminated with different amines in the presence of  $\text{TiCl}_4$  and  $\text{NaBH}_3\text{CN}$ . A preferred overall reaction scheme for the synthesis of labeled amines is illustrated below:



wherein R' is H, linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl, R" is linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl, and R and R1 are as defined above.

5           [<sup>11</sup>C]-labeled ketones and [<sup>11</sup>C]-labeled amines provide valuable PET tracers in various PET studies. In an embodiment of the present invention, it provides kits for use as PET tracers comprising [<sup>11</sup>C]-labeled ketones and/or [<sup>11</sup>C]-labeled amines.

Such kits are designed to give sterile products suitable for human  
10 administration, e.g. direct injection into the bloodstream. Suitable kits comprise containers (e.g. septum-sealed vials) containing the adrenergic interfering agent and precursor of the adrenergic imaging agent.

The kits may optionally further comprise additional components such as  
15 radioprotectant, antimicrobial preservative, pH-adjusting agent or filler.

By the term "radioprotectant" is meant a compound which inhibits degradation reactions, such as redox processes, by trapping highly-reactive free radicals, such as oxygen-containing free radicals arising from the radiolysis of water. The  
20 radioprotectants of the present invention are suitably chosen from: ascorbic acid, para-aminobenzoic acid (i.e. 4-aminobenzoic acid), gentisic acid (i.e. 2,5-dihydroxybenzoic acid) and salts thereof with a biocompatible.

By the term "antimicrobial preservative" is meant an agent which inhibits the  
25 growth of potentially harmful micro-organisms such as bacteria, yeasts or moulds. The antimicrobial preservative may also exhibit some bactericidal properties, depending on the dose. The main role of the antimicrobial preservative(s) of the present invention is to inhibit the growth of any such micro-organism in the pharmaceutical composition post-reconstitution, i.e. in the radioactive diagnostic  
30 product itself. The antimicrobial preservative may, however, also optionally be used to inhibit the growth of potentially harmful micro-organisms in one or more components of the kit of the present invention prior to reconstitution. Suitable antimicrobial preservatives include: the parabens, i.e., ethyl, propyl or butyl paraben



or mixtures thereof; benzyl alcohol; phenol; cresol; cetrimide and thiomersal.  
Preferred antimicrobial preservative(s) are the parabens.

5 The term "pH-adjusting agent" means a compound or mixture of compounds  
useful to ensure that the pH of the reconstituted kit is within acceptable limits  
(approximately pH 4.0 to 10.5) for human administration. Suitable such pH-adjusting  
agents include pharmaceutically acceptable buffers, such as tricine, phosphate or  
TRIS [i.e. tris(hydroxymethyl)aminomethane], and pharmaceutically acceptable bases  
such as sodium carbonate, sodium bicarbonate or mixtures thereof. When the ligand  
10 conjugate is employed in acid salt form, the pH-adjusting agent may optionally be  
provided in a separate vial or container, so that the user of the kit can adjust the pH as  
part of a multi-step procedure.

By the term "filler" is meant a pharmaceutically acceptable bulking agent  
15 which may facilitate material handling during production and lyophilisation. Suitable  
fillers include inorganic salts such as sodium chloride, and water soluble sugars or  
sugar alcohols such as sucrose, maltose, mannitol or trehalose.

### Examples

20

The invention is further described in the following examples which are in no  
way intended to limit the scope of the invention.

#### Example 1 – Experimental Setup

25

[<sup>11</sup>C]Carbon dioxide was produced by the Scanditronix MC-17 cyclotron at  
the Uppsala Research Imaging Solution AB using the <sup>14</sup>N(p,α)<sup>11</sup>C reaction with 17  
Mev protons in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.1%  
oxygen (AGA. Oxygen 4.8). [<sup>11</sup>C]Carbon monoxide was produced by reducing  
30 [<sup>11</sup>C]carbon dioxide in a zinc furnace at 400 °C using a remote controlled work  
station.

Liquid chromatographic analysis (LC) was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV-detector in series with a  $\beta^+$ -flow detector. The following mobile phases were used: 0.05 M ammonium formate, pH 3.5 (A1) and acetonitrile (B1), acetonitrile/H<sub>2</sub>O: 50/7 (B2), methanol (B3) and 0.01 M formic acid in H<sub>2</sub>O (A2). For analytical LC, a Jones Chromatography Genesis C<sub>18</sub>, 4  $\mu$ m, 250  $\times$  4.6 mm (i.d.) column was used with a flow of 1.5 ml/min. For semi-preparative LC, a Jones Chromatography Genesis C<sub>18</sub>, 4  $\mu$ m, 250  $\times$  10 mm (i.d.), column was used with a flow of 4 ml/min. Synthia, an automated synthesis system, was used for LC injection and fraction collection. Data collection and LC control were performed using a Beckman System Gold chromatography software package.

Radioactivity was measured in an ion chamber, Veenstra Instrumenten bv, VDC-202. For coarse estimations of radioactivity during production, a portable dose-rate meter was used, Längenäs Eltekniska AB.

#### Example 2 – Synthesis of [Carbonyl-<sup>11</sup>C] ketones

Tetrakis(triphenylphosphine)palladium(0) (5.0 mg, 4.3  $\mu$ mol) was placed in a vial (1 mL). The vial was flushed with nitrogen and the contents were dissolved in THF (200  $\mu$ L). Aryl triflate (30.8  $\mu$ mol) and LiBr (10  $\mu$ L of 0.46 M solution in THF, 4.6  $\mu$ mol) were added. The mixture was shaken until the solution was homogenous. Aryl- or alkylboronic acid (49.2  $\mu$ mol) was dissolved in THF (100  $\mu$ L) and added to the solution of palladium complex, triflate and lithium bromide just before use. The resulting mixture was injected into the injection loop of the apparatus from where the appropriate volume (200  $\mu$ L) was transferred under pressure (35 Mpa) to the micro-autoclave, pre-charged with [<sup>11</sup>C]carbon monoxide in helium. The micro-autoclave was heated (150 °C) for 5 min. The crude product was transferred to a pre-evacuated, septum-fitted vial (5 mL). The micro-autoclave was filled with THF (200  $\mu$ L) and emptied into the collection vial. The radioactivity was measured before and after the vial was purged with nitrogen. The solvent volume was reduced to less than 0.2 mL by heating at 75 °C and purging with nitrogen. Acetonitrile/water mixture (1:1 2 mL) was added and the resulting solution was injected on the semi-preparative LC. The

identity and radiochemical purity of the collected fraction were assessed by analytical LC.

### 5      Example 3 – Synthesis of $^{11}\text{C}$ -Amines

[ $^{11}\text{C}$ ]Carbonylation was performed as described above using tetrakis(triphenylphosphine)-palladium(0) (5.0 mg, 4.3  $\mu\text{mol}$ ), aryl triflate (30.8  $\mu\text{mol}$ ) and aryl- or methylboronic acid (49.2  $\mu\text{mol}$ ). The crude product was transferred to a pre-evacuated, septum-fitted vial (5 mL) and the radioactivity was measured. The vial was purged with nitrogen to remove the unreacted [ $^{11}\text{C}$ ]carbon monoxide and the radioactivity was measured again. Titanium tetrachloride (500  $\mu\text{L}$  of 1M solution in  $\text{CH}_2\text{Cl}_2$ , 0.5 mmol) and amine (0.13 mmol) were added and the mixture was heated for 3 min at 65  $^\circ\text{C}$ . Sodium cyanoborohydride (500  $\mu\text{L}$  of 1M solution in MeOH, 0.5 mmol) was added and heated for additional 3 min at the same temperature. The reaction was quenched with slow addition of aqueous sodium hydroxide (500  $\mu\text{L}$  of 2M aqueous solution) and filtered. The volume of the filtrate was reduced to 1 mL by heating at 60  $^\circ\text{C}$  and purging with nitrogen. The crude product was analysed with HPLC in presence of small amount of non radioactive reference compound for the identification of the product. The radiochemical yield was determined by multiplying the product purity by trapping efficiency.

### Specific Embodiments, Citation of References

25      The present invention is not to be limited in scope by specific embodiments described herein. Indeed, various modifications of the inventions in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

30      Various publications and patent applications are cited herein, the disclosures of which are incorporated by reference in their entireties.

**What is claimed is:**

1. A method for labeling synthesis of ketones, comprising:

- 5 (a) providing a high pressure reaction chamber having a liquid inlet and a gas inlet in a bottom surface thereof,
- (b) providing a solution to be labeled comprising a triflate, a boronic acid mixed with a transitional metal complex,
- (c) introducing a carbon-isotope monoxide enriched gas-mixture into the reaction  
10 chamber of the UV reactor assembly via the gas inlet,
- (d) introducing at high pressure said solution mixed with transition metal complex into the reaction chamber via the liquid inlet,
- (e) waiting for a predetermined time while the labeling synthesis occur, and
- (f) removing the labeled ketones from the reaction chamber.

15

2. A method of claim 1, wherein the carbon-isotope monoxide enriched gas-mixture is produced by a method comprising:

- (a) providing carbon-isotope dioxide in a suitable carrier gas,
- (b) converting carbon-isotope dioxide to carbon-isotope monoxide by introducing  
20 said gas mixture in a reactor device,
- (c) trapping carbon-isotope monoxide in a carbon monoxide trapping device, wherein carbon-isotope monoxide is trapped but not said carrier gas, and
- (d) releasing said trapped carbon-isotope monoxide from said trapping device in a well defined micro-plug, whereby a volume of carbon-isotope monoxide enriched  
25 gas-mixture is achieved.

25

3. A method of claim 1, wherein the carbon-isotope is  $^{11}\text{C}$ ,  $^{13}\text{C}$ , or  $^{14}\text{C}$ .

4. A method of claim 1, wherein the carbon-isotope is  $^{11}\text{C}$ .

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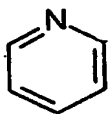
5. A method of claim 1, wherein the step of introducing the solution to be labeled mixed with a transitional metal complex is performed using a pressure that is about 80 times higher than the pressure before the introduction, in order to maintain a pseudo one-phase system.

6. A method of claim 1, wherein the step of waiting a predetermined time comprises adjusting the temperature of the reaction chamber to enhance the labeling synthesis.

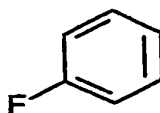
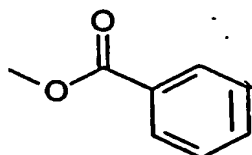
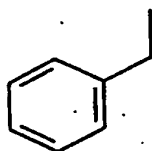
7. A method of claim 1, wherein the transitional metal complex is a palladium metal complex.

8. A method of claim 1, wherein the triflate has a formula  $R1-OTf$ , wherein  $R1$  is linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl.

9. A method of claim 8, wherein  $R1$  is selected from  $C_6H_5$ ,  $4-CH_3O-C_6H_4$ ,  $4-CH_3-C_6H_4$ ,  $4-NO_2-C_6H_4$ ,  $C_{10}H_7$  or



10. A method of claim 1, wherein the boronic acid has a formula  $RB(OH)_2$ , wherein  $R$  is linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl.



or theinyl.

12. A method of claim 1, wherein the solution to be labeled is further mixed with lithium bromide to facilitate the reaction.

5

13. A labeled ketone synthesized according to a method of claim 1 having a formula of  $R1-C^*O-R$ , wherein  $*$  is labeled carbon position, and  $R1$  and  $R$  are independently linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl.

10

14. A method of labeling synthesis of amines comprising:

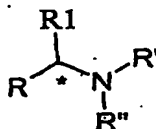
- (a) synthesizing a labeled ketone of claim 13,
- (b) reductive aminate the labeled ketone with different amines in the presence of  $TiCl_4$  and  $NaBH_3CN$ .

15

15. A method claim 14, wherein the amines of step (b) having a formula  $R'R''NH$ , wherein  $R'$  is  $H$ , linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl,  $R''$  is linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl.

20

16. A labeled amine synthesized according to method 14 having a formula of



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wherein  $*$  is labeled carbon position, and  $R1$  and  $R$  are independently linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl,  $R'$  is  $H$ , linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl,  $R''$  is linear or cyclic alkyl or substituted alkyl, aryl or substituted aryl.

30

17. A kit for PET study comprising a carbon-isotope labeled ketone of claim 13.

18. A kit for PET study comprising a carbon-isotope labeled ketone of claim 16.

19. A kit of claim 18, further comprising radioprotectant, antimicrobial preservative, pH-adjusting agent or filler.

5 20. A kit of claim 19, wherein the radioprotectant is selected from ascorbic acid, para-aminobenzoic acid, gentisic acid and salts thereof.

21. A kit of claim 19, wherein the antimicrobial preservative is selected from the parabens, benzyl alcohol, phenol, cresol, cetrimide and thiomersal.

10 22. A kit of claim 19, wherein the pH-adjusting agent is a pharmaceutically acceptable buffer or a pharmaceutically acceptable base, or mixtures thereof.

23. A kit of claim 19, wherein the filler is inorganic salts, water soluble sugars or sugar alcohols.

15

**Abstract**

Methods and reagents for synthesizing carbon-isotope labeled ketones and amines by carbonylation via Suzuki coupling reaction using carbon-isotope labeled carbon monoxide are provided. The resultant carbon-isotope labeled ketones and amines are useful as radiopharmaceuticals, especially for use in Positron Emission Tomography (PET). Associated kits for PET studies are also provided.



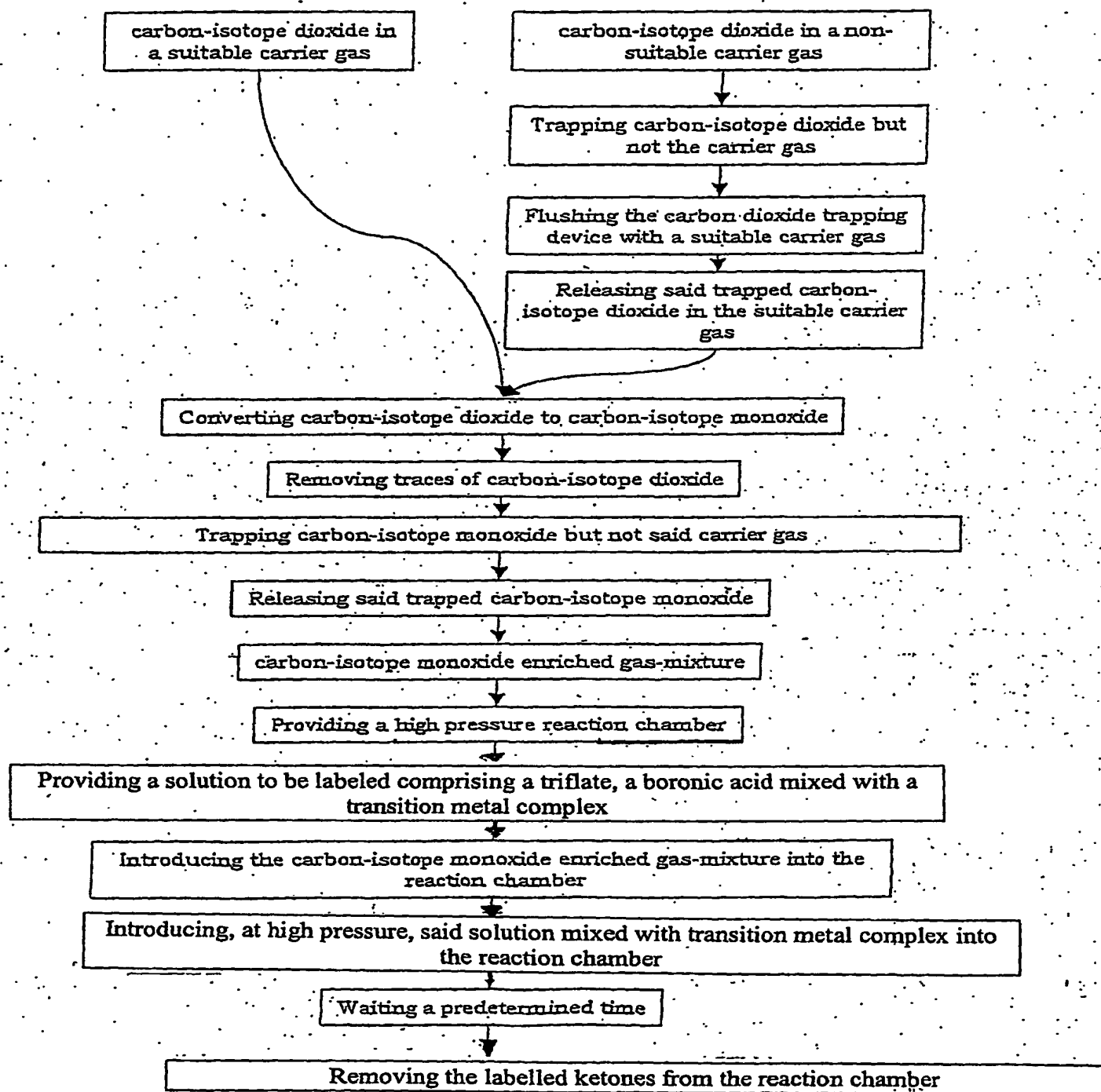


Fig. 1

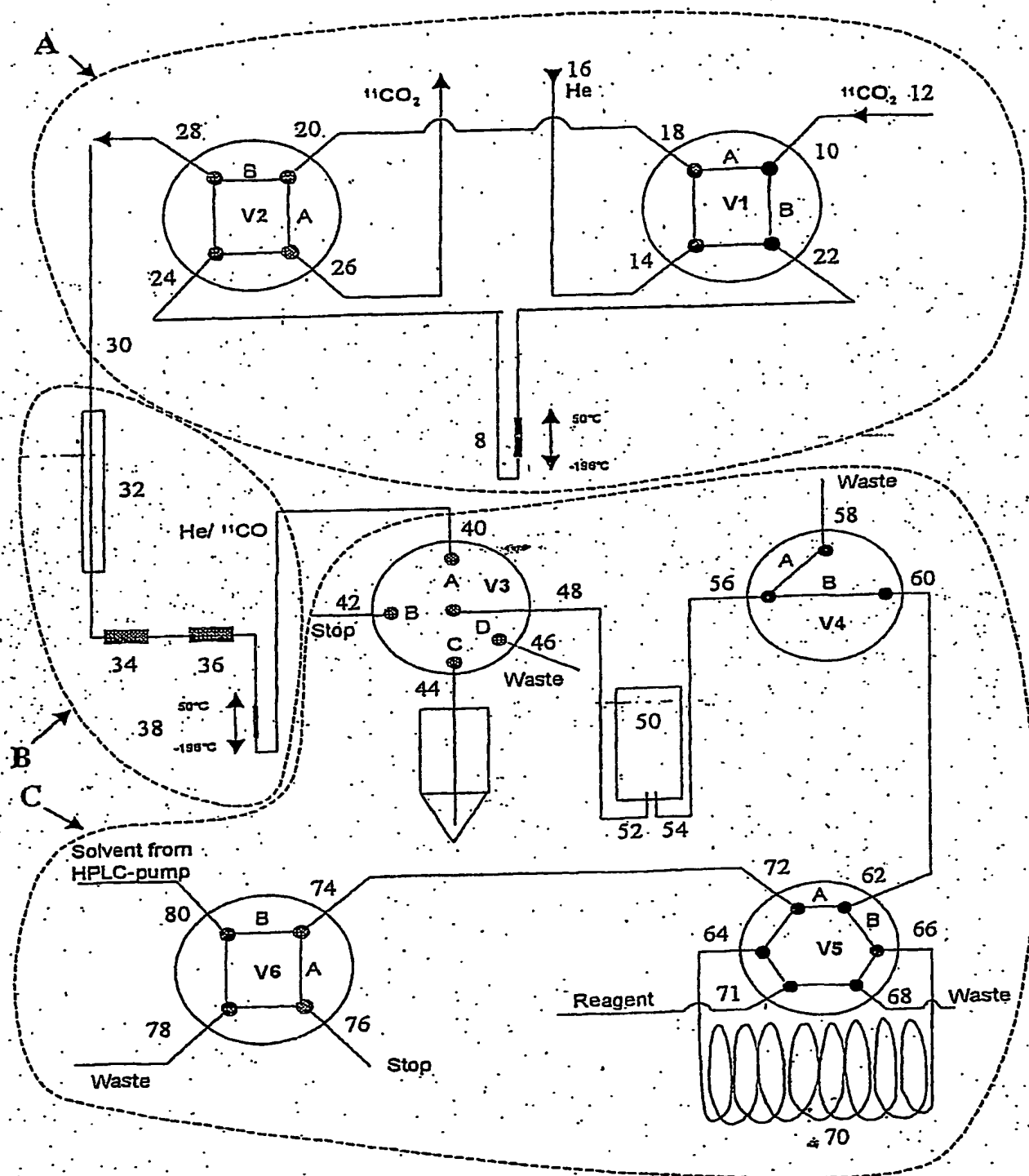


Fig. 2

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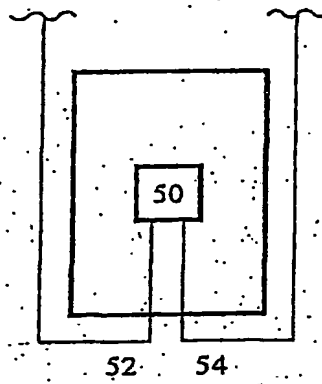


Fig. 3a

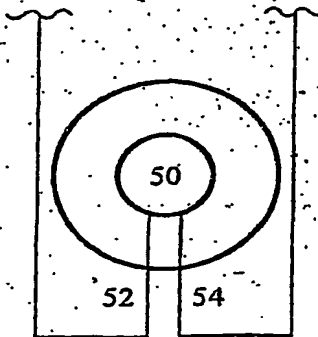


Fig. 3b

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